

Patent Claims

1. A method for the detection of nucleic acid sequences is hereby characterized in that the following steps are conducted:

- a) at least one nucleic acid is bound to a solid phase;
- b) probe molecules are hybridized to the nucleic acids in a sequence-specific manner, whereby the probe molecules are provided with a cleavable bond and a mass label, which is specific for the probe molecule;
- c) removal of the unhybridized probe molecules;
- d) contacting of the hybridized probe molecules with a matrix, which cleaves said cleavable bonds and at the same time serves as the matrix in a MALDI mass spectrometer;
- e) detection of the mass label at those positions where the nucleic acid was bound.

2. The method according to claim 1, further characterized in that the nucleic acid sequences to be detected are DNA sequences and particularly sequences that are variable between different nucleic acids and that contain SNPs, point mutations, deletions, inversions or insertions.

3. The method according to claim 1, further characterized in that the nucleic acid sequences to be

detected are chemically pretreated DNA sequences and particularly sequences treated with bisulfite, which serve for the detection of DNA methylation at specific CpG positions.

4. The method according to one of claims 1 to 3, further characterized in that the nucleic acid is amplified prior to binding to the solid phase, whereby this can be preferably produced by means of enzymatic primer extension, PCR, rolling circle amplification, ligase chain reaction or other method.

5. The method according to one of the preceding claims, further characterized in that the solid phase is the sample support of a mass spectrometer.

6. The method according to claim 5, further characterized in that the solid-phase surface is comprised of silicon, glass, polystyrene, aluminum, steel, iron, copper, nickel, silver, or gold.

7. The method according to one of claims 1 to 4, further characterized in that the solid phase can be utilized in the sample support of a MALDI mass spectrometer.

8. The method according to one of the preceding claims, further characterized in that several nucleic acids are disposed on the solid phase surface in the form of a rectangular or hexagonal grid.

9. The method according to one of the preceding claims, further characterized in that the probe molecules are DNA or modified DNA.

10. The method according to one of the preceding claims, further characterized in that the probe molecules are LNA, PNA or corresponding hybrids thereof, also with DNA or modified DNA.

11. The method according to claim 9, further characterized in that after the hybridization, the probe molecules are modified enzymatically by primer extension.

12. The method according to claim 9, further characterized in that after the hybridization, the probe molecules are modified enzymatically by ligation.

13. The method according to one of claims 11 or 12, further characterized in that the mass label is first joined with the probe molecule as a consequence of the enzymatic modification.

14. The method according to one of the preceding claims, further characterized in that the mass label bears a single positive or a single negative charge.

15. The method according to one of the preceding claims, further characterized in that the mass of a label differs each time by at least 1 Da from the masses of all other labels used in one experiment.

16. The method according to claim 3, further characterized in that the probe molecules comprise at least one CG, TG or CA dinucleotide.

17. The method according to one of claims 3 or 16, further characterized in that in step b), the amplicates are hybridized on two classes of probe molecules, each with at least one member, whereby the probe molecules of the first class preferably hybridize to the sequence which arises from the chemical treatment of the genomic DNA, if a cytosine to be investigated was present in the methylated state in the genomic DNA and whereby the probe molecules of the second class preferably hybridize to the sequence which arises from the chemical treatment of the genomic DNA, if a cytosine to be investigated was present in the unmethylated state in the genomic DNA.

18. The method according to one of claims 3 or 16, further characterized in that in step b), a hybridization is produced on two classes of probe molecules, each with at least one member, whereby the probe molecules of the first class preferably hybridize to the sequence which arises from the chemical treatment of the genomic DNA, if a cytosine to be investigated was present in the methylated state in the genomic DNA and less preferably to the sequence which arises from the chemical treatment of the genomic DNA, if a cytosine to be investigated was present in the unmethylated state in the genomic DNA, and whereby the oligomers of the second class hybridize to the amplicate to be investigated essentially independently of the methylation of said specific cytosine in the genomic DNA.

19. The method according to one of claims 3 or 16, further characterized in that in step b), a hybridization is produced on two classes of probe molecules, each with at least one member, whereby the probe molecules of the first class preferably hybridize to the sequence which arises from the chemical treatment of the genomic DNA, if a cytosine to be investigated was present in the unmethylated state in the genomic DNA and less preferably to the sequence which arises

from the chemical treatment of the genomic DNA, if a cytosine to be investigated was present in the methylated state in the genomic DNA, and whereby the oligomers of the second class hybridize to the amplicate to be investigated essentially independently of the methylation of said specific cytosine in the genomic DNA.

20. The method according to one of the preceding claims, wherein the nucleic acid was obtained from cell lines, blood, sputum, stool, urine, cerebrospinal fluid, tissue embedded in paraffin (for example, tissue from eyes, intestine, kidney, brain, heart, prostate, lung, breast or liver), histological slides or all possible combinations thereof.

21. Use of a method according to one of the preceding claims for the diagnosis and/or prognosis of adverse events for patients or individuals, whereby these adverse events belong to at least one of the following categories: undesired drug effects; cancer diseases; CNS malfunctions, damage or disease; symptoms of aggression or behavioral disturbances; clinical, psychological and social consequences of brain damage; psychotic disturbances and personality disorders; dementia and/or associated syndromes; cardiovascular disease, malfunction and damage; malfunction, damage or disease of the gastrointestinal tract; malfunction, damage or disease of the respiratory system; lesion, inflammation, infection, immunity and/or convalescence; malfunction, damage or disease of the body as [a consequence of] an abnormality in the development process; malfunction, damage or disease of the skin, the muscles, the connective tissue or the bones; endocrine and metabolic malfunction, damage or disease; headaches or sexual malfunction.

22. Use of a method according to one of the preceding claims for distinguishing cell types or

tissues or for investigating cell differentiation.

23. A kit, comprising a solid phase for immobilizing the nucleic acid, probe molecules, as well as components for conducting the mass-spectrometric measurement as well as instructions for conducting a method according to one of the preceding claims.